Breast Irradiation in Ductal Carcinoma *In Situ*

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Rezumat

Există dovezi puternice și consistente că iradierea întregului sân după intervenția chirurgicală conservatoare scade semnificativ riscul de recidive mamare ipsilaterale, *in situ* sau invazive, susținând rolul său stabilit la pacienții cu carcinom ductal *in situ* (CDIS). În așteptarea publicării rezultatelor complete ale studiului randomizat BIG 3-07/TROG 07.01, se recomandă suplimentarea iradierii la nivelul patului tumoral alături de iradierea întregului sân în prezența caracteristicilor clinico-patologice nefavorabile, fiind susținută utilizarea programelor de hipofracționare a întregii doze de iradiere. Deoarece datele publicate care susțin utilizarea iradierii parțiale adjuvante mamare la pacienții cu DCIS cu risc scăzut sunt limitate, aplicarea sa în afara studiului ar trebui limitată la pacienții definiți de ghidurile internaționale și naționale ca având risc scăzut. În cele din urmă, pacienții cu risc scăzut ar putea să nu obțină beneficii semnificative din punct de vedere clinic în urma radioterapiei, iar cercetările privind determinarea profilului molecular sunt în curs de desfășurare pentru a îmbunătăți precizia prognosticului și a ghida posibilitatea omiterii radioterapiei, în siguranța, după intervenția chirurgicală conservatoare.

Cuvinte cheie: carcinom ductal *in situ*, CDIS, radioterapie, hipofracționare doze de iradiere, volumul țintă de radiație

Abstract

There is strong and consistent evidence that whole breast irradiation after breast conserving surgery significantly decreases

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the risk of ipsilateral breast events, *in situ* or invasive, underpinning its established role in patients with ductal carcinoma *in situ* (DCIS). Pending publication of the full results of BIG 3-07/TROG 07.01 randomised trial, addition of tumour bed boost to whole breast irradiation is recommended in the presence of adverse clinical-pathologic features, and the use of moderately hypofractionated whole breast dose-fractionation schedules is supported. As published data supporting the use of adjuvant partial breast irradiation in patients with low-risk DCIS are limited, its off-study application should be limited to low-risk patients defined by international and national guidelines. Finally, low-risk patients may not derive clinically meaningful benefits from radiation therapy and research on molecular profiling is ongoing to improve prognostic precision and guide safe omission of radiation therapy after breast conserving surgery.

Key words: ductal carcinoma *in situ*, DCIS, radiation therapy, radiation dose-fractionation, radiation target volume

Introduction

The diagnosis of ductal carcinoma *in situ* (DCIS), a heterogeneous group of neoplastic lesions confined to the breast ducts has increased substantially since the large-scale implementation of mammographic screening programs, accounting for 25% of screen-detected breast cancer (1). DCIS is a non-obligate precursor lesion to invasive breast cancer. Breast cancer mortality after a diagnosis of DCIS is low. A Surveillance, Epidemiology, and End Results database analysis of more than 100,000 patients with DCIS reported 10 and 20-year risks of breast cancer-specific mortality of 1.1% and 3.3%, respectively (2). However, invasive local recurrence after treatment is associated with a 75% increase in the risk of mortality (3,4). Thus, the principal goal of treatment of DCIS is to minimise the risk of progression to invasive breast cancer.

There remain significant variations in the treatment of DCIS primarily as a consequence of the lack of clear markers of disease recurrence and invasive progression in the context of its varying malignant potential and clinical behaviour. This review focuses on relevant literature on the evolving roles of adjuvant radiation therapy after breast conserving surgery in the multidisciplinary management of patients with DCIS.

Radiation Therapy after Breast Conserving Surgery

An Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview of four randomised trials comparing whole breast irradiation versus no radiation after breast conserving surgery involving 3,729 patients has been the major source of level 1 evidence that informs radiation therapy practice in DCIS (Table 1) (5).

The EBCTCG meta-analysis provided strong and consistent evidence that whole breast irradiation after breast conserving surgery halved the rate of ipsilateral breast events, *in situ* or invasive cancer (rate ratio 0.46, standard error [SE] 0.05, 2P<0.00001) (5). It significantly reduced the absolute 10-year risk of any local recurrence by 15.2% (12.9% versus 28.1%, 2P<0.00001). This treatment benefit was observed regardless of the age at diagnosis, extent of breast conserving surgery, margin status, use of tamoxifen, and pathologic characteristics including tumour grade, comedo-necrosis and tumour size. In the cohort of patients with low grade DCIS of up to 20 mm resected with negative margins, the absolute reduction in the 10-year risk of ipsilateral breast events was 18.0% (SE 5.5, 12.1% vs 30.1%, 2P = 0.002). Despite the substantial reduction in local recurrences, there was no difference in 10-year breast cancer

Table 1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview of randomised trials comparing breast conserving surgery with and without adjuvant whole breast irradiation

	No.	Negative surgical margin	Breast radiation therapy	Median follow-up
NSABP B17 (6-8)	798	87%	50 Gy (2 Gy/F) 9% with boost	16.5 years
EORTC 10853 (9-12)	918	84%	50 Gy (2 Gy/F) 5% with boost	10.4 years
SweDCIS (13-15)	1011	81%	50 Gy (2 Gy/F) (80%) or 48 Gy (2.4 Gy/F) (13%) or 54 Gy (2 Gy/F) (7%) Boost not recommended	8.4 years
UK-ANZ (16)	1002	100%	50 Gy (2 Gy/F) Boost not recommended	4.8 years

*EORTC, European Organisation for Research and Treatment of Cancer; F, fraction; Gy, Gray; NSABP, National Surgical Adjuvant Breast and Bowel Project; UK-ANZ, United Kingdom-Australia-New Zealand

mortality or overall survival. These data underpin the routine use of adjuvant radiation therapy after breast conserving surgery in many patients with DCIS to optimise local disease control.

Long-term follow-up of the randomised trials confirmed earlier findings of the effects of adjuvant whole breast irradiation on local recurrence and breast cancer mortality (Table 2) (17).

Dose-fractionation in Whole Breast Irradiation for DCIS

The dose-fractionation used in the randomised trials of DCIS comparing breast conserving surgery with or without adjuvant whole breast irradiation was primarily the conventional schedule 50 Gy administered in 2-Gy daily

fractions over 35 days without a tumour bed boost (Table 1).

The EBCTCG meta-analysis showed that the 10-year local recurrence rates after adjuvant whole breast irradiation remained high at up to 20.7% in selected patient subgroups, including patients who were aged under 50 years or had high grade DCIS (5). The potentially greater burden of residual disease at the tumour bed may require a higher radiation dose to minimise the risk of local recurrence. In a 20-year report of a randomised trial in invasive breast cancer, the addition of tumour bed boost (16 Gy in 2-Gy daily fractions) to whole breast irradiation (50 Gy in 2-Gy daily fractions) significantly improved local control (HR=0.65; $p<0.0001$) but also increased severe fibrosis (1.8% without boost versus 5.2% with boost) (20). Two

Table 2. Long-term results of randomised trials comparing breast conserving surgery with and without adjuvant whole breast irradiation

	Median follow-up (years)	Local recurrence (%)		Breast cancer mortality (%)	
		No WBI	WBI	No WBI	WBI
NSABP B-17 (3)	17.3	35	20	3	5
EORTC 10853 (4)	15.8	31	18	4	5
SweDCIS (18)	17.0	32	20	4	4
UK-ANZ (19)	12.7	23	9	3	2
EBCTCG (5)	8.9	28	13	4	4

*EBCTCG, Early Breast Cancer Trialists' Collaborative Group; EORTC, European Organisation for Research and Treatment of Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project; UK-ANZ, United Kingdom-Australia-New Zealand; WBI, whole breast irradiation

large non-randomised studies showed inconsistent results in the effect of tumour bed boost in DCIS (21,22).

Hypofractionated radiation therapy involving the use of fewer, larger fractions than conventional dose-fractionation is under active investigation to improve access, timeliness and cost-effectiveness of treatment delivery. The 10-year results of multiple large-scale randomised trials in invasive breast cancer have consistently demonstrated that moderately hypofractionated adjuvant whole breast irradiation of 40.0–42.5 Gy in 15–16 fractions, given over three weeks, is at least as safe and effective as conventionally fractionated whole breast irradiation (23–25). Another randomised trial in both invasive breast cancer (n=1608) and DCIS (n=246) showed no significant difference in the 9-year local recurrence rates between conventionally fractionated and hypofractionated whole breast irradiation for patients with DCIS (26).

Results of the international randomised phase III study of radiation doses and fractionation schedules in 1608 patients with non-low risk DCIS treated with breast conserving surgery (BIG 3-07/TROG 07.01) were recently presented in abstract form (27). In this trial, non-low risk DCIS was defined as (a) patient age <50 years, or (b) patient age ≥50 years plus one or more risk factors for local recurrence (palpable tumour, multifocal disease, tumour size of 15 mm or larger, intermediate or high nuclear grade, central necrosis, comedo histology and/or surgical margin of less than 10 mm). Patients were randomised to have a tumour bed boost (16 Gy in 8 daily fractions) or no boost following conventional (50Gy in 25 daily fractions) or hypofractionated (42.5 Gy in 16 daily fractions) whole breast irradiation. At a median follow-up of 6.6 years, tumour bed boost significantly reduced local recurrence, and there was no difference in local recurrence rates between the conventionally fractionated and hypofractionated whole breast irradiation groups. Publication of the full efficacy results is pending. In the reported international comparison of cosmetic outcomes, tumour bed boost was associated with a >2-fold risk of

cosmetic deterioration ($P<0.001$), and hypofractionated whole breast irradiation achieved statistically similar 3-year cosmesis compared to conventional whole breast irradiation ($P\geq 0.18$) (28). In addition, the adverse cosmetic impact of the boost was not significantly associated with whole breast dose-fractionation schedules (interaction $P\geq 0.30$).

The panel of the St. Gallen International Consensus Guidelines for treatment of early breast cancer recommended use of a tumour bed boost in patients with larger areas of DCIS or other factors associated with increased risk of recurrence including surgical margins < 2 mm and presence of comedo-necrosis, but not in low-risk cases (29). The panel also supported the use of moderately hypofractionated schedules, which were as effective as conventional schedules in DCIS.

Radiation Target Volume for DCIS

Partial breast irradiation after breast conserving surgery provides the opportunity for integrating a reduced target volume limited to the primary tumour bed and safe acceleration of radiation treatment usually in one week or less to improve the convenience of care. The treatment techniques include interstitial or balloon catheter-based brachytherapy, intraoperative RT or external beam radiation therapy. In comparison to invasive breast cancer, there are limited data from institutional series and randomised trials that included patients with DCIS.

The NSABP B-39/RTOG 0413 randomised trial comparing accelerated partial breast irradiation with conventionally fractionated whole breast irradiation after breast conserving surgery was primarily a trial of invasive breast cancer but included 1,031 patients (24%) with DCIS (30). Although partial breast irradiation did not meet the criteria for equivalence to whole breast irradiation in controlling local recurrences, the absolute difference in the 10-year local recurrence rates was low (4.6% versus 3.9%).

The RAPID trial randomised 2,135 patients including 381 patients with DCIS to

adjuvant external beam-based partial breast irradiation (38.5 Gy in 10 fractions delivered twice per day over 5–8 days) or whole breast irradiation (31). At a median follow-up of 8.6 years, the 8-year cumulative local recurrence rates were 3.0% (95% CI 1.9–4.0) in the partial breast irradiation group and 2.8% (1.8–3.9) in the whole breast irradiation group. Although partial breast irradiation was shown to be non-inferior to whole breast irradiation in preventing local recurrence, it was associated with an increase in moderate late toxicity and adverse cosmesis. Thus, these results do not support adoption of the RAPID partial breast irradiation schedule in routine practice, and further investigation is necessary to refine the dose-fractionation regimen.

The American Society for Radiation Oncology (ASTRO) consensus statement on accelerated partial breast irradiation supported the use of partial breast irradiation in patients with low-risk DCIS, which included all of the following characteristics: screen-detected, size ≤ 2.5 cm, low to intermediate nuclear grade, and resected with negative margins of ≥ 3 mm (32).

Although the limited data support the use of partial breast irradiation in patients with low-risk DCIS, further investigations in refining patient selection and radiation dose-fractionation are required. In the interim, a pragmatic approach is to limit off-study application of partial breast irradiation to low-risk patients defined by international and national guidelines, guided by patient preference.

Selective Omission of Radiation Therapy in DCIS

DCIS is a heterogeneous disease with substantial variations in local recurrence risks and hence absolute benefits of radiation therapy after surgery in individual patients. Importantly, despite the substantial reduction in local recurrences, adjuvant radiation therapy was not associated with improvement in breast cancer mortality or overall survival (5). With advances in multidisciplinary care and biomarker-directed risk stratification, selected patients with low-risk DCIS may not derive clinically meaningful benefits from adjuvant whole or partial breast irradiation. The key challenge in patient selection for safe omission of adjuvant radiation is the lack of consensus on markers for defining low-risk DCIS.

The EBCTCG meta-analysis defined a potentially favorable subgroup based on tumor size < 20 mm, low nuclear grade and negative surgical margins but did not identify a low-risk patient subgroup (5). In this subgroup of 291 patients, the 10-year ipsilateral breast event rates were 30.1% without adjuvant radiation therapy and 12.1% with whole breast irradiation.

Table 3 summarises the prospective studies designed to define low-risk DCIS using clinical and pathologic characteristics.

The Eastern Cooperative Oncology Group (ECOG) trial E5194 was an observational study of breast conserving surgery without

Table 3. Prospective studies of omission of radiation therapy after breast conserving surgery in DCIS

	No.	Size (mm) (median)	Margins (mm)	Grade	Tamoxifen (%)	WBI	FU (years)	LR (%)	P
<i>Harvard (33)</i>									
	143	≤ 25	≥ 10	1-2	No	No	10	15.6	-
<i>ECOG-ACRIN E519 (34,35)</i>									
Cohort 1	561	≤ 25 (6)	≥ 3	1-2	31	No	12	14.4	0.003
Cohort 2	104	≤ 10 (7)	≥ 3	3	24	No		24.6	
<i>NRG/RTOG 9804 (36,37)</i>									
No WBI	298	≤ 25 (5)	≥ 3	1-2	66	No	13.9	15.1	0.0007
WBI	287	≤ 25 (5)	≥ 3	1-2	58	Yes		7.1	

*Grade 1, low grade; grade 2, intermediate grade; grade 3, high grade; WBI, whole breast irradiation; LR, local recurrence

radiation therapy in two cohorts of patients with DCIS (*Table 3*) (34,35). The 12-year local recurrence rates, *in situ* or invasive, were 14.4% in the first cohort and 26.6% in the second cohort. Despite the selection of patients with more favourable clinical and pathologic characteristics, the recurrence rates were observed to increase over the 12-year follow-up without plateau. These results support the routine use of adjuvant radiation therapy in patients with high grade DCIS. The 10-year recurrence rate of almost 15% in patients with low or intermediate grade DCIS and a median tumour size 6 mm may not be sufficiently low to justify routine omission of radiation.

NRG/ROG 9804 is a randomised trial that investigated the impact of whole breast irradiation versus observation after breast conserving surgery in women with putative good-risk DCIS (*Table 3*) (36,37). The study closed early due to slow accrual after enrolling 636 patients. At a median follow-up of 13.9 years, the 15-year cumulative incidence of local recurrence, invasive or *in situ*, was 7.1% (95% CI, 4.0-11.5) in the whole breast irradiation group versus 15.1% (95% CI, 10.8-20.2) in the no radiation group ($P=0.0007$; $HR=0.36$; 95% CI, 0.20 to 0.66). The corresponding cumulative incidence of invasive local recurrence was 5.4% (95% CI, 2.7-9.5) with radiation therapy versus 9.5% (95% CI, 6.0-13.9) without radiation ($P=0.027$; $HR=0.44$; 95% CI, 0.21-0.91).

The long-term results of prospective studies do not necessarily underline an absolute indication for radiation therapy but serve to guide individualised treatment decision making taking into account patient preference, competing causes of mortality and risks of radiation therapy. The panel of the St. Gallen International Consensus Guidelines supports omission of radiation therapy in patients aged 70 years or over with DCIS bearing low risk features (29).

Biomarkers of Recurrence in DCIS

The current literature highlights the challenges in defining the characteristics of

low-risk DCIS using conventional histopathology to guide individualised therapy. Molecular profiling using multigene expression assays is being investigated to improve the prognostic precision for DCIS.

The Oncotype DX DCIS Score is a 12-gene prognostic test that provides individual estimates of 10-year local recurrence risk after breast conserving surgery. In an analysis involving 327 participants treated with breast conserving surgery alone in the ECOG-ACRIN study, pre-defined risk categories of DCIS Score were significantly associated with local recurrence (38). In patients with a low, intermediate, and high DCIS Score, the 10-year local recurrence risks, invasive or *in situ*, were 10.6%, 26.7% and 25.9%, respectively. The corresponding risks for invasive recurrence were 3.7%, 12.3% and 19.2%, respectively. The DCIS Score was validated in a population-based cohort (39). It was also shown in a subsequent study to be predictive of benefit of radiation therapy (40).

Decision Score is a biologic signature derived from cancer-related genes and clinical-pathologic factors (age, tumor size, margin status, palpability) (41). It was shown to be prognostic for recurrence risk with a 10-year invasive breast cancer risk of 4% and ipsilateral breast event risk of 7% in patients treated without radiation therapy. The corresponding figures were 15% and 23% in the Elevated Risk Group. Decision Score was also shown to be predictive of radiation therapy benefit with significant benefit for the Elevated Risk Group but not the Low Risk Group.

Promising results notwithstanding, data regarding the utility of molecular profiling in DCIS remain limited. The cost-effectiveness of molecular profiling-based, risk-adapted use of radiation therapy has not been shown from a population perspective. Further validation of these results is ongoing.

Conclusion

There is strong and consistent evidence that whole breast irradiation after breast

conserving surgery significantly decreases the risk of ipsilateral breast events, *in situ* or invasive, underpinning its established role in patients with DCIS. Pending publication of the full results of BIG 3-07/TROG 07.01 randomised trial, addition of tumour bed boost to whole breast irradiation is recommended in the presence of adverse clinical-pathologic features, and the use of moderately hypofractionated whole breast dose-fractionation schedules is supported. As published data supporting the use of adjuvant partial breast irradiation in patients with low-risk DCIS are limited, its off-study application should be limited to low-risk patients defined by international and national guidelines. Finally, low-risk patients may not derive clinically meaningful benefits from radiation therapy and research on molecular profiling is ongoing to improve prognostic precision and guide safe omission of radiation therapy after breast conserving surgery.

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Conflict of Interest

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